IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Jacques DUMAS et al.		Confirmation No.:	9096
Serial No.:	09/838,286	Examiner:	KWON, Brian Yong S.
Filed:	April 20, 2001	Group Art Unit:	1614

Title: HETEROARYL UREAS CONTAINING NITROGEN HETERO-ATOMS AS P38 KINASE INHIBITORS

SECOND REPLY BRIEF

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Second Examiner's Answer mailed Novenber16, 2007, Appellant's respond as follows:

This Second Reply Brief is presented in response to the following new points of argument raised in the Second Examiner's Answer on pages 18-31 to support the rejection under 35 USC § 112, first paragraph.

1) On page 18, lines 11-15, the Second Examiner's Answer states:

> Determining if any particular compound would treat any particular disease would require synthesis of the compound, formulation into a suitable dosage form and subjecting it to clinical trials ...to treat said disease conditions or to testing them in an assay known to be correlated to clinical efficacy of such treatment.

No evidence has been presented which even suggests that the assays disclosed in the specification are insufficient to demonstrate the claimed compounds are effective in treating diseases mediated by p38. In addition, Appellants submit the Examiner's requirement that the assay be "known to be correlated to clinical efficacy of such treatment" is met by the knowledge of the inventors, who are skilled in the art. In addition, it is not necessary to perform such assays or subject these compounds to clinical trials to satisfy 35 USC § 112, first paragraph. As discussed in the Brief on Appeal, imposing such requirements is inconsistent with case law such

as *In re Marzocchi*, 439 F.2d 220, 169 U.S.P.Q. 367 (CCPA 1971) and *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436, 1442 (Fed. Cir. 1995.

2) Pages 18-28 of the Second Examiner's Answer describe various causes, manifestations, mechanisms and treatments for inflammation. In referring to these various causes, manifestations, mechanisms and treatments for inflammation, page 28, lines 3-5, of the Second Examiner's Answer states:

> The above list is by no means complete, but demonstrates the extraordinary breadth of causes, mechanisms and treatment (or lack thereof) for inflammation. It establishes that it is not reasonable [for] any agent to able to treat inflammation, furthermore various diseases mediated by p38.

Theses various causes, manifestations, mechanisms and treatments bear no relevance as to whether these diseases are linked by a common cellular mechanism that allows mediation by p38. The various causes, manifestations, mechanisms and treatments for inflammation present no reason to doubt the findings within any of the 75+ publications cited in the specification linking each of the diseases specified to TNF–α production or MMP production, which are inhibited by the inhibition of p38. There is also no reason to doubt the animal models of inflammatory diseases that have shown p38 inhibitors to be active which are mentioned on page 5, lines 21-26, of the specification.

3) On page 28, lines 8-12, the Second Examiner's Answer states:

> Appellant takes the position that numerous prior art references of record, namely USP 5,932,576, USP 5,593,992,USP5,593,991 and USP 5,658.903 describe urea compounds of a similar structure and similar broad utility.

It is <u>not</u> Appellant's position USP 5,932,576, USP 5,593,992,USP5,593,991 and USP 5,658.903 describe urea compounds of a similar structure to those claimed. These references are not cited in an IDS as the examiner suggests. They were mentioned in the Brief on Appeal to demonstrate that "those skilled in the art have recognized and claimed that <u>certain</u>

compounds can be effective for treating all types of diseases mediated by p38." Applicants do not maintain the compounds of these references have a similar structure to those claimed.

As stated in the Reply Brief, Appellants do maintain most of the of the numerous prior art references which have cited in an IDS and made of record describe urea compounds of a similar structure and similar broad utility, including the p38 inhibitor BIRB-796. BIRB-796 has been used in clinical trials to treat various inflammatory diseases. In finding the art unpredictable, Examiner has not acknowledged or considered the broad teachings in the art relating to similar ureas with similar activity, including those relating to BIRB-796.

4) On page 28, lines 14-17, the Second Examiner's Answer states:

> Unlike the appellant's argument, none of the cited references provide similar urea structure of the instant compounds. Nor provides any specific guidance for determining the particular administration of regimens (e.g., dosages, timing, administration routes, etc...) necessary to treat all of the various diseases mediated by p38.

First, it is unnecessary for these references to provide such a disclosure since the disclosure within the specification is adequate. Dosages are disclosed on pages 26-27 of the specification and modes of administration are disclosed on pages 22-26 of the specification. No evidence has been presented that these disclosures are deficient.

Second, if such disclosures are absent from the cited US patents, this suggests that disclosures of dosages, timing and administration routes are not necessary to satisfy the requirements of 35 USC 112, first paragraph.

Third, the Examiner has not explained why the urea p38 inhibitor BIRB-796 is not similar to the compounds claimed and its use in clinical trials provides no guidance in using the compounds of this invention.

5) On page 29, lines 10-12, the Second Examiner's Answer states:

> It is not enough to rely on in vitro studies where, as here, a person having ordinary skill in the art has no basis for perceiving those studies as constituting recognized screening procedures with clear relevance to utility in humans or animals. See Ex Parte Maas, 9USPQ2d 1746.

The inventors herein include PhD researchers (7) and technicians employed by the assignee, a major pharmaceutical company. The inventors represent skilled artisans in this field and they have found the assay employed in the specification adequate to indicate utility in humans and animals. No evidence has been presented to refute these findings and no evidence has been presented one skilled in the art would doubt these teachings.

Unlike the application in the case of Ex Parte Maas, 9USPQ2d 1746(BPAI, 1989), the prior art discussed in the present application describes a correlation between TNF-α and MMP and various diseases. In addition, the specification discloses the following correlation at page 5:

> Inhibitors of p38 are active in a number of standard animal models of inflammatory diseases, including carrageenan-induced edema in the rat paw, arachadonic acid-induced edema in the rat paw, arachadonic acid-induced peritonitis in the mouse, fetal rat long bone resorption, murine type II collagen-induced arthritis, and Fruend's adjuvant-induced arthritis in the rat. Thus, inhibitors of p38 will be useful in treating diseases mediated by one or more of the above-mentioned cytokines and/or proteolytic enzymes.

6) On page 30, lines 1-5, the Second Examiner's Answer states:

> Gura et al, cited for evidentiary purposes, teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and further teach that since formal screening began in1955, many thousands of drugs have shown activity in either in cell or animal models but only 39 have actually been shown to be useful for chemotherapy,

Appellants respectfully disagree with this interpretation of the teachings within Gura et al. The efforts by researchers Gura et al speaks of is in trying to "develop a new generation of more effective and less toxic anticancer drugs..." The effort is not in finding efficacious drugs as the examiner suggests but in finding **more** effective drugs. Gura et al do not teach that only 39 drugs have been shown to be useful for chemotherapy but that "only 39 ... have won approval from the US Food and Drug Administration." A drug may not win approval from the FDA although efficacious where it is less active than existing drugs.

7) On page 30, lines 6-8, the Second Examiner's Answer states:

> It is noted that the pharmaceutical [art] is unpredictable, requiring each embodiment to be individually assessed for physiological activity.

As discussed within the Brief on Appeal in citing *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436, 1442 (Fed. Cir. 1995), an applicant is not required to test the claimed compounds in their final use or win approval at the FDA to satisfy the enablement requirement of 35 USC §112, first paragraph.

8) On page 30, lines 9-11, the Second Examiner's Answer states:

> Also with regard to unpredictability, Johnson et al, also cited for evidentiary purposes, teach that the in vivo activity of 39 different agents in a particular histology in a tumor model did not correlate to activity in the same human cancer.

Appellants respectfully disagree with this interpretation of the teachings of Johnson et al. First, Appellants note that Johnson et al teaches in the Summary on page 1424 that "in vivo activity in a particular histology in a tumour model did not **CLOSELY** correlate with activity in the same human cancer histology" (emphasis added). Johnson et al clearly teaches that there was some correlation between the tumor model and clinical response. Second, Appellants note that Johnson et al considered a positive response in phase II clinical trials involved "an objective 50 % reduction in tumour size in at least 20 % of the patients." page 1425. Therefore, the correlation Johnson et al investigated with regard to tumor models was not for clinical efficacy alone but for a significant clinical response. This is well beyond the requirements of 35 USC §112.

The teachings of Gura et al and Johnson et al do not raise any doubt with regard to ability of the compounds claimed to treat p38 mediated diseases and it is not necessary that each compound claimed be tested in clinical trials or win approval from the FDA to meet the statutory requirements under 35 USC §112.

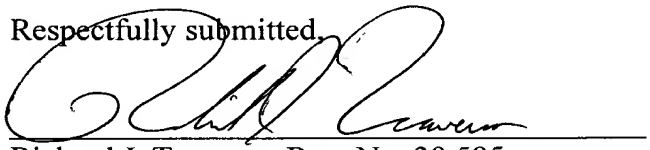
9) On page 31, lines 4-11, the Second examiner's Answer states;

> The Examiner acknowledges that the Office does not require the present[ion] of (all) working examples to be present in the disclosure of the invention (see MPEP 2164.02) However, given the highly unpredictable state of the art and given the applicant does not provide sufficient guidance or direction as to how to use the full scope of the presently claimed invention without undue experimentation, the Office would require appropriate disclosure, in the way of scientifically sound reasoning or the way of concrete examples, as to why the data shown is a reasonably representative and objective showing that it was commensurate in scope with and thus, adequately enables the use of the elected species for the full scope of the presently claimed subject matter.

Applicants maintain that the showing of p38 inhibition for the exemplified compounds is commensurate in scope with the claims. The claims recite the use of compounds of formula I (A-D-B). Examples of compounds with each value for "A" (trifluoromethylpyridyl, t-butylpyridyl, isoquinolinyl, and quinolinyl) and "D" (urea) have been synthesized and tested for p38 activity. Examples of compounds with values for "B" (phenyl, naphthyl and -L-$(ML^1)_q$) have also been synthesized and tested for p38 activity. The values for B which are exemplified are representative of all values for B, particularly in view of prior disclosures of aryl and hetaryl urea p38 inhibitors such as WO 98/52558, WO 99/32110, WO99/32111, WO 32463 and WO 00/41698. In these publications, various aryl and hetaryl urea p38 inhibitors with various substituents are disclosed and tested for p38 inhibition. The examiner has not identified any deficiencies in the disclosure with regard to any of the compounds claimed.

For the reasons stated above and in the First Reply Brief and Brief on Appeal, Appellants respectfully submit the subject matter of the claims on appeal satisfy the requirements of 35 U.S.C. §112, first paragraph. Therefore, Appellants respectfully request the outstanding rejection be reversed.

Respectfully submitted,



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